in one or more genes encoding a protein essential for viral replication as broadly claimed.

Fields Virology, Chapter 72, "Herpes Simplex Viruses and Their Replication" (Exhibit A) reviews the replication of HSV. Table 1 of that chapter lists HSV genes, their products, functions, and whether or not they are "*dispensable for replication in cell culture.*" Thirty-six genes are listed as being required for replication in cell culture, including ICP4, ICP8, and ICP27; the functions of many of these genes have been elucidated. Not all of these are required for viral genome replication, as claimed, but are required, for example, for viral entry (see e.g., gH). Applicants have found that inactivation of three out of three genes tested (ICP4, ICP8, and ICP27) resulted in a functional mutant, and two of the three (ICP8 and ICP27) produced an isotype shift. Undue experimentation is therefore not required to practice the invention. A skilled practitioner need only follow the methods and examples described in the specification to test each of the remaining genes (mutation of ICP27 is on pages 17-22 of the specification; mutation of ICP8, on pages 29-35; methods to determine ability of mutants to induce subclass shift is on pages 46-52).

Furthermore, the Federal Circuit has held that claims may encompass some inoperative species, as long as the number of inoperative species does not become significant and force one of ordinary skill into undue experimentation in order to practice the invention (Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 224 USPQ 409, at 414 (Fed. Cir. 1984)). That is not the case here. Applicants have tested three genes, and have found that two of them conformed to the limitations of (1) rendering the mutant genome replication defective, and (2) effecting an antibody subclass shift (claims 1-3, 12-14, 16 and 17). It would be a simple matter for one of ordinary skill in the art to test the remaining genes that are listed in Fields Virology as being essential for growth in cell culture. Further, each mutant tested (including the mutant characterized by the ICP4

inactivation) induced immunological protection (see claims 9 and 25-41). Thus, these claims are enabled.

Applicants submit that the specification is fully enabling, and respectfully request that the rejection on 35 U.S.C. § 112 grounds be withdrawn.

Claim Rejections under 35 U.S.C. § 102(a)

Claims 1-3, 5-7, 9, 12-14, 16-20, 22, 25, 26, 31-34, 36-39, and 41 are rejected under 35 U.S.C. § 102(a) as being anticipated by Inglis et al. (WO 92/05263).

Inglis et al. disclose a mutant HSV which has a defect in a gene essential for viral entry (the gH gene, see Fields Virology, last line of page 2233), and a vaccine comprising said mutant. The Examiner notes that Inglis et al. do not specifically characterize gH as being essential for virus replication *per se*, but states that this would be a reasonable conclusion by one skilled in the art, because gH is required for the normal course of infection, and is therefore also required generally for overall replication of the virus. The claims, as amended, are not anticipated by this mutant.

Applicants would like to point out that the invention of Inglis et al. comprises mutations in genes for infection-essential proteins required in the normal course of viral infection (paragraph 2, page 5 of Inglis et al.), while the present invention comprises mutations in the genes required for the replication of the viral genome. That is, the viral mutants of both inventions have the ability to enter a cell initially, and both are incapable of infecting other cells in turn. But the two inventions accomplish this in completely different ways. The mutant of Inglis et al. may infect a cell initially, can replicate its genome normally, and can package viral particles, but cannot make a protein required for the viral infection of new host cells (thereby producing non-infectious progeny).

The mutants of the present invention on the other hand, also infect a cell, but are incapable of completely replicating their

g nomes upon infection. Unlike the mutants of Inglis et al. they cannot create new viral particles.

Applicants clearly state that in the present invention, "... the mutation renders the virus replication defective. The mutated virus is live in the sense that it retains the ability to infect target cells in the host to be protected. Infection will not produce progeny ..." (Lines 2-5 of page 3 of the specification).

To more particularly point out the differences between these two inventions, however, Applicants have amended the claims to specify "viral genome replication" rather than "viral replication." Furthermore, claims 12-22, drawn to methods of treating an immunomodulatory disease are not described by this reference and are thus novel. It is respectfully submitted that the intended use of a novel method of therapy can carry patentable weight (In re Naylor, 152 USPQ 106 (CCPA 1966); In re Shetty, 195 USPQ 755 (CCPA 1977)).

Applicants therefore respectfully request that the rejection on § 102(a) grounds be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 4, 8, 15, 21, 27, 35, and 40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Inglis et al. (WO 92/05263) and further in view of McCarthy et al. (J. Virol. 63(1):18-27 (1989)). The Examiner states that Inglis et al. suggest using "...viral mutants that are inactivated for genes involved in viral genome replication *for an immunogenic response*..." (emphasis added), citing pages 8-10 therein.

On page 10, Inglis et al. state that "[t]he gene should preferably be one which is required later in infection." (page 10 of Inglis et al., lines 17-18). Furthermore, in a 1994 paper, (J. Virology 68:927-932; reference AY3 of the Information Disclosure Statement filed August 30, 1994) by Farrell, McLean, Harley, Efstathiou, Inglis, and Minson (Inglis and Minson are two

of the thre inventors of the WO 92/05263 application), the authors discuss work by others in this area.

> The magnitude of T-cell responses to these mutants was *proportional* to the extent to which viral gene expression occurred in infected cells. However, the replication-defective mutants used in their study were deficient in the expression of all or some of the late gene products, many of which are known to be targets for antibodies and T cells .... *In contrast*, infection of cells with the phenotypically gH-positive SC16ΔhH mutant results in *a replicative cycle that is normal in all respects except that the progeny are noninfectious*.

Farrell et al., page 931, middle paragraph (emphasis added).

Therefore, Inglis et al. clearly view mutations in the genes responsible for viral genome replication as undesirable in that the immunogenic response of these genes is required for immunological protection. That is, the reference teaches that the deletion of Early and Immediate Early genes (e.g., genes required for genome replication) will be less effective as vaccines than the deletion of the Late genes (e.g., the gH gene). These are precisely the genes that are inactivated in Applicants' invention. It was unexpected from these teachings that deletion of these same genes would protect against lethal infection, or provide a treatment of genital herpes, to the extent described in the specification (see pages 43-46 and 59-61). Inglis et al., therefore teach away from using the mutated genes that are the core of the Applicants' invention.

McCarthy et al. teach the use of the HSV-1 ICP27 mutant, which is replication incompetent. However, McCarthy et al. do not discuss the immunogenic response produced by this mutant, nor the possibility of using such mutants as vaccines. The Applicants' invention is therefore not obvious in view of the combination of McCarthy et al. and Inglis et al., because the second advises against deleting Immediate Early genes, of which ICP27 is one.

Claims 4, 8, 15, 21, 29, 35, and 40 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Inglis et al. (WO 92/05263) and further in view of Gao et al. (J. Virol. 63(12):5258-5267 (1989)). Gao et al. studied the HSV ICP8 gene. Like McCarthy et al., Gao et al. do not discuss the immunogenic responses of the mutants, nor their potential usefulness as vaccines.

As stated above, Inglis et al. warn the practitioner away from using genes that are expressed early in infection, and neither McCarthy et al. nor Gao et al. suggest any motivation for using mutants of ICP27 or ICP8 as a vaccine. The Federal Circuit has stated that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." (In re Geiger, 815 F.2d 686, 688, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987)). Applicants submit that when the cited references are combined, they not only fail to produce the present invention, but in fact teach away from it. Applicants therefore respectfully request that the rejection on this basis be withdrawn.

CONCLUSION

Applicants have amended claims 1, 5, 9, 12, 17, 18, 25, 32, and 37 to more particularly point out and distinctly claim the subject matter they regard as the invention, and to correct a minor typographical error in claim 32.

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue.

If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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